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Synthesis and DNA cleavage studies of novel quinoline oxime esters

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ABSTRACT

New 2-chloro-3-formyl quinoline oxime esters were synthesized by the reaction of 2-chloro-3-formyl quinoline oximes with various benzoyl chlorides in the presence of triethyl amine and dichloromethane at 0 °C. The DNA photo cleavage studies of some new oxime esters were investigated by neutral agarose gel electrophoresis at different concentrations (40 μM and 80 μM). Analysis of the cleavage products in agarose gel indicated that few of quinoline oxime esters (**3d–i**) converted into supercoiled pUC19 plasmid DNA to its nicked or linear form.

Various oximes served as important synthetic intermediates, and have been employed as starting materials for the preparation of many types of biologically active heterocyclic compounds. Some of the pyridine oximes are tested for cardiovascular system.[1] Oximes possess considerable biological activities, their prominent effects are for example, antidepressants, analgesic, anti-inflammatory, fungicidal, herbicides, hepatitis, antiulcer and antiandrogens activity.[2]

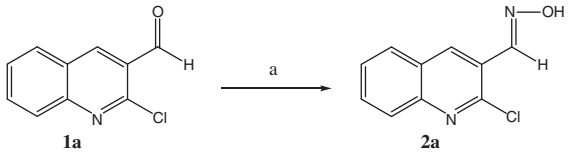
In particular, quinoline oximes and their derivatives represent an important class of organic molecules that attract the interest of both synthetic and medicinal chemists. The members of the quinoline oximes family are attracting increased attention due to their, antidepressants, sedatives, anticonvulsive, analgesic, anti-inflammatory, cytotoxic, antitumor, anti-HIV, and fungicidal, herbicidal activity.[3]

Recently, photodynamic therapy (PDT) is an emerging method of non-invasive treatment of cancer in which drugs like photofrin shows localised toxicity on photoactivation at the tumour cells leaving the healthy cells unaffected.[4] There has been increased interest in the discovery and investigation of compounds that damage DNA upon irradiation, also known as photonucleases,[5] exhibit a large potential for therapeutically applications such as photodynamic chemotherapy,[6] because they are often inert until activated by light and, thus, the DNA-damage may be controlled both in a spatial and temporal sense. Importantly, the type and the efficiency of the photo cleavage reaction will depend on the binding affinity and the binding site that the photonuclease occupies.

Hence, in view of the synthetic, biological importance of quinolines and in continuation of our work on heterocycles,[7] here in we report the synthesis of quinoline oxime esters and evaluated their nucleolytic activities.

Several methods have been developed for the preparation of quinoline oxime derivatives.[8] The most common method is the reaction of 2-chloro-3-formyl-quinoline (**1a**) with hydroxylamine hydrochloride, in which the condensation of an amine with an aldehyde is carried out in the presence of ethanol leads to the aldoxime **2a** with a yield of 80–90%.[9] Substituted quinoline oxime **2a** was synthesized according to the literature procedure shown in Scheme 1.[10] The condensation of 2-chloro-3-formyl-quinoline (**1a**) with hydroxylamine hydrochloride and Et_3N gave white shiny coloured oxime **2a** with 98% yield. Reaction of the mixture of oxime **2a** with substituted benzoyl chlorides followed by Et_3N in the presence of dichloromethane gave **3a–i** shown in Scheme 2,[10] Table 1. The desired products were obtained on an average yield of 90% after purification. Their structures were established with IR, ^1H NMR, ^{13}C NMR and mass spectrometry.

The quinoline oxime esters (QOE) were photolyzed at 365 nm, at concentration of 40 μM in the presence of pUC-19 DNA.[7] Solutions



1a **2a**

Scheme 1. Reagents and condition: (a) $NH_2OH{\cdot}HCl$, Et_3N, EtOH, rt.

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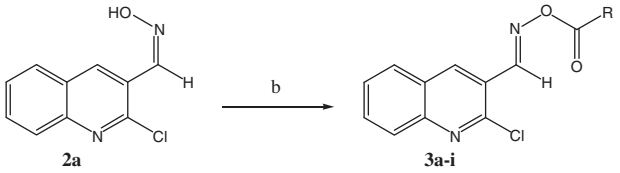

Scheme 2. Synthesis of quinoline oxime esters. Reagents and condition: (b) RCOCl, Et_3N, CH_2Cl_2, 0 °C.

Table 1
Synthesis of quinoline oxime esters

Entry [a]	R	Time (h)	Yield[b] (%)	Mp (°C)
3a	C_6H_5	1	92	169–171
3b	*p*-$OCH_3C_6H_4$	1	92	156–158
3c	*p*-OHC_6H_4	1	75	162–164
3d	*p*-ClC_6H_4	1	88	159–161
3e	*p*-BrC_6H_4	1	95	180–182
3f	*p*-$NO_2C_6H_4$	1	90	149–151
3g	*p*-FC_6H_4	1	95	150–152
3h	*o*-FC_6H_4	1	85	150–152
3i	*m*-dinito-C_6H_3	1	92	148–150

[a] All the products were characterised by elemental analysis, ^1H NMR, ^{13}C NMR and mass spectral data.
[b] Yields of isolated products.

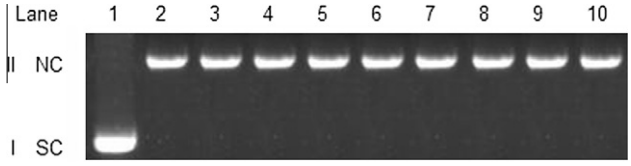

Figure 1. Photo cleavages of DNA by QOE were irradiated with UV light at 365 nm. Supercoiled DNA runs at position I (SC) and nicked DNA at position II (NC). Lane 1: control DNA (with out compound), Lane 2: 40 μM (**3a**), Lane 3: 40 μM (**3b**), Lane 4: 40 μM (**3c**), Lane 5: 40 μM (**3d**), Lane 6: 40 μM (**3e**), Lane 7: 40 μM (**3f**), Lane 8: 40 μM (**3g**), Lane 9: 40 μM (**3h**), Lane 10: 40 μM (**3i**).

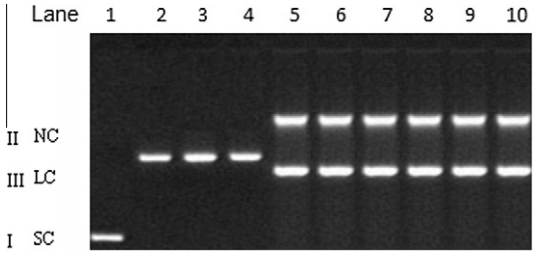

Figure 2. Light-induced cleavage of DNA by QOE of 80 μM were irradiated with UV light at 365 nm. Supercoiled DNA runs at position I (SC), linear DNA at position III (LC) and nicked DNA at position II (NC). Lane 1: control DNA (with out compound), Lane 2: 80 μM (**3a**), Lane 3: 80 μM (**3b**), Lane 4: 80 μM (**3c**), Lane 5: 80 μM (**3d**), Lane 6: 80 μM (**3e**), Lane 7: 80 μM (**3f**), Lane 8: 80 μM (**3g**), Lane 9: 80 μM (**3h**), Lane 10: 80 μM (**3i**).

were irradiated for 2 h, in 1:9 DMSO/Trisbuffer (20 μM, pH 7.2) at 365 nm. Cleaving ability was determined quantitatively by the effectiveness in converting super coiled plasmid DNA (Form I) to nicked circular (Form II) as shown in Figures 1 and 2, at the concentration of (40, 80 μM). In Figure 2, control experiments did not show any apparent cleavage of DNA (lane 1). The studies show that the synthesized oxime esters can be induced to photoextrusion under conditions required for DNA cleavage producing intermediates capable of hydrogen abstraction. With increasing concentration of respected derivatives (lanes 2 and 3), the amount of Form I of pUC19 DNA diminish gradually, whereas Form II increases. Under comparable experimental conditions, oximes (Fig. 2), exhibit more effective DNA cleavage activity compared to halogen derivatives. Further studies in detail are currently underway to clarify the mechanism.

Supercoiled DNA was completely converted to nicked and linear DNA at the concentrations of 80 μM (**3d–i**). But, in the same run the halogen derivatives are not completely converted to nicked and linear DNA (**3a–c**). Higher concentrations were not examined because of the precipitation of oximes in the reaction mixture. This reveals that QOE are capable to accelerate the cleavage of plasmid DNA dramatically, which may be due to the electron donating groups and further studies in detail are currently underway to clarify the cleavage mechanism.

In conclusion, we have reported the simple, convenient and high yielding synthesis of 2-chloro-3-formyl quinoline oxime esters. The electrophoretic data of 2-chloro-3-formyl quinoline oxime esters showed concentration and substitution dependent nucleolytic activities. The electron donating groups are highly reactive radical. These radicals abstracts hydrogen atoms efficiently at C-4′ of 2-deoxyribose in B-DNA. The molecules having halogen and nitro groups are less active. The generated nitrogen and oxygen radical are capable to accelerate the cleavage of plasmid DNA in halogen and nitro substituted QOE.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.12.037.

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reaction mixture was evaporated under reduced pressure to give the residue, to which H_2O (25 mL) was added and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $NaSO_4$, filtered, and evaporated to give the crude white product, the crude compound was recrystalize with *n*-hexane–EtOAc (1:1) gave the pure 98% of white shiny oxime compound.; (d) *General procedure for the synthesis of oxime esters*: To a solution of **2a** (500 mg, 1.8 mmol) in CH_2Cl_2 (30 mL) was added benzoyl chloride (0.5 mL, 2.3 mmol) in the presence of Et_3N (0.9 mL, 2.3 mmol) at 0 °C. After being stirred for 1 h, the reaction mixture was quenched with 1 N HCl and extracted with CH_2Cl_2 to give the residue, which was washed with saturated $NaHCO_3$ aqueous solution and brine and dried over anhydrous $NaSO_4$. Purification by flash column chromatography on silica gel *n*-hexane–EtOAc (1:1) gave the pure **3a** (480 mg,92%) as colorless needles.